REMARKS

Claims 73-85 are pending. All claims are rejected for failure to comply with the enablement requirement of 35 U.S.C. 112, first paragraph. Applicant herein responds to the Examiner's rejection of claims 73-85 for lack of enablement.

Withdrawn Objections and/or Rejections

Applicant acknowledges the Examiner's withdrawal of the objections to the specification with respect to the title and informalities.

IDS Submitted Herewith

Applicant submits herewith an IDS containing the references mentioned herein.

Rejection of the Claims Under 35 U.S.C. § 112, first paragraph

Claims 73-85 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not describe in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner argues that the enablement standard is not satisfied because of the lack of a relationship between MRR and bone disease. Specifically the Examiner states the "existence of a relationship between MRR and bone diseases are what is called into question."

The Examiner indicates that the assay to detect a compound which binds MRR is enabled. Specifically the Examiner states that the "in vitro assay to detect compounds which bind to a given protein, a MRR protein in this case, in a biological sample is provided. Note, this procedure is routine and not in dispute." Applicant appreciates the Examiner's acknowledgment that the assay itself is not of issue.

Applicant respectfully traverses the 35 U.S.C. 112, first paragraph rejection asserting that the teachings in the Specification sufficiently enable one of ordinary skill in the art to make and/or use the instant invention without undue experimentation when considered in light of the disclosure of the present Specification, knowledge of those of skill in the art, and the disclosure of the art.

First, the Specification clearly demonstrates the nexus between MRR and bone disorders. The Examiner acknowledges on page 5, paragraph 10 that "MRR may be involved in bone formation." Therefore the Examiner's acknowledgement suggests that there is a nexus between MRR and *bone formation*, but the Examiner seems to doubt that MRR is involved in *bone disorders*. The Specification teaches that bone disorders are characterized by defects in bone formation as a result of aberrant deposition, absorption, or configuration of bone tissue. For example osteoporosis is characterized by a decrease in bone density. Furthermore, the Specification teaches that MRR is expressed at high levels in developing bone tissue. This is evident throughout the Application and emphasized by the results conveyed in Figures 3 and 4, indicating that MRR is highly expressed in developing bone. Bone disorders are characterized by an imbalance in bone production and/or reabsorption processes, "when the breakdown and formation of bone are not in balance (i.e., when more bone is broken down than is formed) there is bone loss. Most diseases of the skeleton are due to such an imbalance, resulting in systemic or local bone loss." Rodan. *Bone*. 1992; 13:S3-S6. Thus, it is reasonable to conclude that modulation of bone formation, (e.g., enhanced formation and/or decreased absorption through modulation of MRR as described in the Specification) would benefit one with decreased bone density, e.g., osteoporosis.

The present Application claims methods for identification of compounds useful for modulating an MRR mediated bone disorder. The Specification clearly describes that

compounds which bind to MRR and modulate MRR may be useful in modulating an MRR mediated bone disorder, in accordance with the nexus between MRR function and bone formation. As acknowledged by the Examiner, the *in vitro* assay steps are routine, thus not undue experimentation. Thus, Applicant submits one of ordinary skill in the art would certainly be able to sufficiently practice the claimed invention without undue experimentation in view of Applicant's disclosure and the knowledge in the art.

The Examiner, in citing multiple references relating to MRR, argues that the art does not lead one to conclude that that MRR is involved in bone related disorders. Applicant fully agrees with the Examiners conclusion and reiterates that it is the *Applicant's invention* that MRR is involved in bone related disorders. It is the Applicant's efforts that suggest MRR's involvement in bone related disorders. Thus, the teachings of the prior art regarding cloning and ligand binding studies, in combination with the teachings present in the Application relating to MRR and bone related disorders fully enable one to practice the method to identify an agent that binds to MRR as a candidate compound for use in modulating an MRR mediated bone-related disorder.

Applicant respectfully reasserts the Examiner has not established a reasonable basis to question the enablement provided for the claimed invention. The Examiner has not made a sufficient showing, based on findings of fact why one of skill in the art could not practice the invention that is claimed. The many publications relied upon by the Examiner, which the Examiner suggests teaches the contrary to MRR's involvement in bone related disorders, do not support a reasonable basis to question the enablement provided for the claimed invention. These publications simply teach a possible alternative function of MRR. In fact, Applicant herein emphasizes that MRR's involvement in bone related disorders is what the Applicant regards as

the basis for the claimed invention. Furthermore, not a single reference relied upon by Examiner states that MRR *is not* involved in bone disorders.

In fact, the homology to the melatonin receptor and the significant art teaching melatonin's role in bone-related disorders support the Applicant's assertion that MRR is involved in bone-related disorders. MRR shares high homology to the melatonin receptors and Applicant's identification of its localization within developing bone indicate that it is likely involved in the bone formation and bone disorders and performs a similar function to the melatonin receptor.

The art teaches that melatonin is involved in bone formation and bone disorders, e.g., osteoporosis. For a review of melatonin and its effects on bone formation and bone disorders see Cardinali *et al. J. Pineal Res.* 2003; 34:81-87, and references therein. Others have discovered that melatonin promotes the differentiation of osteoblasts, mineralization of the matrix and increases expression of essential bone proteins. See Roth *et al. J. Biol. Chem.* 1999; 274: 22041-22047, and references therein. Furthermore, Roth *et al.* also suggests that the decrease in melatonin levels that occur with age may contribute to osteoporosis and that treatment with melatonin may prevent this disorder. Additionally, Cardinali *et al.* teaches that melatonin increases cell proliferation and augments type I collagen synthesis.

Melatonin's effect on bone formation and hence bone disorders is likely similar to estrogen, bone morphogenic proteins and vitamin D3. see McDougall *et al. Endocrinology* 2003; 144(5): 1994-1999; Cardinali *et al. J. Pineal Res.* 2003; 34:81-87; Roth *et al. J. Biol. Chem.* 1999; 274: 22041-22047, and references therein. For example, it is well established that estrogen replacement therapy is effective at ameliorating bone loss associated with hypogonadism. Wiren *et al. J. Endocrinology.* 2002; 175(3):683-694. Furthermore it is also apparent that estrogen stimulates bone formation through the estrogen receptor alpha.

McDougall *et al. Endocrinology* 2003; 144(5): 1994-1999. Similarly, vitamin D and other anti-absorptive agents such as parathyroid hormone, IL-1 and tumor necrosis factor alpha can be used to offset the reabsorptive effects of glucocorticoid treatment that result in bone loss. Rodan, *Bone.* 1992; 13; S3-S6. While these ligands and their coordinating receptors have been shown to be involved in other processes, the action of the receptors (e.g., estrogen receptor, melatonin receptors) has also been shown to play a role in bone formation and resulting bone disorders. Similarly here, the role of melatonin related receptor in bone formation and bone related disorders cannot be put in dispute simply because the Examiner is of the opinion that alternative processes are more believable.

Furthermore, the Examiner states that based upon the art, sequence homology and the expression pattern of MRR would lead to the conclusion that MRR is involved in the modulation of circadian rhythm and reproductive cycles and not involved in bone related disorders. In fact, the art teaches a correlation between circadian rhythm and bone formation. Cardinali *et al.* citing Ostrowska *et al. Neuroendocrinology Letters.* 2001; 22:121-127. Ostrowska *et al.* examined a correlation between 24 hour serum melatonin levels and circadian metabolism of type I collagen in post-menopausal women, discovering a negative correlation between melatonin amplitude rhythm and circadian indicators of collagen metabolism. Thus, the Examiner's argument is not sufficient to support a prima facie case for lack of enablement.

Therefore based upon the support, direction and guidance, the high level of skill of one in the art, and the methodology known in the art, Applicant asserts one of ordinary skill in the art is enabled to make/use the invention without undue experimentation. Reconsideration and withdrawal of the rejection is thus respectfully requested.

Conclusion

Applicant respectfully submits that the present claims are allowable. Should the Examiner find that there are any outstanding issues or that an interview would be helpful to further prosecution of this application, he is invited to telephone the undersigned at his convenience. This paper is being filed timely. No fees or extensions of time are required. In the event any additional extensions of time are necessary, the undersigned hereby authorizes the requisite fees to be charged to Deposit Account No. 501668.

Entry of the remarks made herein is respectfully requested.

Respectfully submitted,

20 May 2003

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